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Non-imidazole Heterocyclic Histamine H_3 Receptor Antagonists

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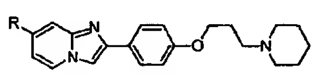
Abstract—Continued exploration of the SAR around the lead imidazopyridine histamine H_3 antagonist **1** has led to the discovery of several related series of heterocyclic histamine H_3 antagonists. The synthesis and SAR of indolizine, indole and pyrazolopyridine based compounds are now described.

Histamine receptors are divided into four subtypes, H_1,[1] H_2,[2] H_3,[3] and H_4,[4] at which histamine exhibits distinct pharmacological effects. Thus histamine plays a role in the pathogenesis of allergic conditions via the H_1 receptor and in gastric acid secretion via the H_2 receptor. H_1 and H_2 receptor antagonists have subsequently proven effective for the treatment of allergic diseases and gastric ulceration, respectively. The discovery of a third histamine receptor, H_3, by Arrang and coworkers,[3] stimulated extensive research which demonstrated that the receptor is a presynaptic autoreceptor on histaminergic neurons and a presynaptic heteroreceptor on non-histamine containing neurons with greatest densities in the central nervous system.[5–9] Consequently many applications have been proposed for H_3 receptor ligands, particularly in the CNS and centrally acting H_3 antagonists may provide novel therapies for neurological disorders such as epilepsy, sleeping disturbances, arousal/vigilance, ADHD and cognition.[10]



1 R = CH_3, K_i = 2 nM
2 R = H, K_i = 6 nM

Earlier, we described[11] a series of imidazopyridines identified via high throughput screening, utilizing the recombinant human H_3 receptor.[12] This afforded a potent and selective H_3 antagonist **1** with good oral bioavailability and blood–brain barrier penetration. Following this discovery we sought to explore replacements for the imidazopyridine nucleus which are the subject of this Letter.

Results

Throughout the study, we chose to retain the piperidinopropyloxyphenyl fragment which is optimal according to our previous results.[11] This piperidinopropyloxyphenyl fragment is also present in the potent non-imidazole H_3 antagonists described by other groups.[13,14] Here, we only address replacements for the imidazopyridine nucleus together with substitutions in the heterocyclic and central phenyl rings. We first turned our attention to removing one of the heterocyclic ring nitrogens to afford indolizines and indoles. Thus the parent indolizine **3** (K_i = 13 nM) exhibited comparable activity to the corresponding imidazopyridine **2** (K_i = 6 nM) (Table 1). A range of simple substitutions were next examined. The attachment of a methyl group was tolerated with the five-membered ring, but with the six-membered ring, a reduction in affinity was observed. This contrasts with the results[11] for the imidazopyridine where analogous substitutions were favorable and suggests a slightly different receptor–ligand interaction for the indolizines. Although substitution in the phenyl ring led to reduced affinity (e.g., **14**), introduction of an additional substituent (e.g., **15**) to impart a steric

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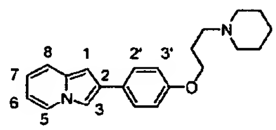
Table 1. Indolizine and aryl ring substituents, oxypropylpiperidine terminus

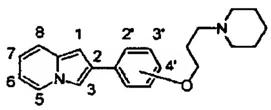


3–15

No.	Substituent	K_i (nM)
3	H	13 (±2.3)
4	1-CH_3	16 (±2.6)
5	3-CH_3	2 (±0.2)
6	5-CH_3	46 (±13.1)
7	6-CH_3	28 (±6.0)
8	7-CH_3	40 (±7.4)
9	8-CH_3	40 (±13.0)
10	1-Ph	40 (±6.2)
11	1-CH_2CH_3	19 (±2.1)
12	3-CH_2CH_3	5 (±1.6)
13	1-CH_2CH_2Ph	37 (±4.1)
14	2′-CH_3	152 (±33.4)
15	2′,1-di-CH_3	11 (±3.2)

K_i values for the human H_3 receptor were determined in house and calculated according to Cheng and Prusoff[15] where $K_i = IC_{50}/(1 + [S]/K_d)$ where [S] = 0.8 nM and K_d = 0.8 nM for [^{3}H]-*N*-methylhistamine. Values are means of three to seven experiments, SEM is given in parentheses.

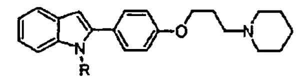
Table 2. Piperidinylpropoxy point of attachment



3, 16 and 17

No.	Substituent	K_i (nM)
3	4′	13 (±2.3)
16	3′	308 (±34.1)
17	2′	236 (±89.9)

interaction between the indolizine and the phenyl ring restored affinity. In the cases where a small substituent was tolerated, larger substituents were examined (e.g., 10–13) and found to be acceptable. However, no improvement in potency was observed. The point of attachment for the piperidinylpropoxy side chain was also examined (Table 2) and a decrease in affinity was observed as the point of attachment was moved from



18, R = H, K_i = 47 (±6.4) nM
19, R = SO_2CH_3, K_i = 16 (±5.9) nM

Figure 1.

para to *meta* or *ortho*. We next prepared the indole analogue **18** recognizing that the indole nucleus contains a more acidic nitrogen than either the imidazopyridine or the indolizine nucleus (the calculated proton affinities of these heterocycles are in ref 16). In this case, a significant reduction in affinity was observed, although the sulfonamide intermediate **19** exhibited high affinity (Fig. 1).

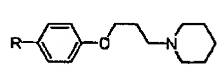
One additional heterocyclic system was also examined, the pyrazolopyridine **20**. In this case, the pyrazolopyridine system exhibited similar affinity to that observed for the imidazopyridine and indolizine system. The potencies for the different heterocycles shown in Table 3 apparently reflect the basicities of the heterocycles and a good correlation between their calculated proton affinities and their binding affinities was observed.[16]

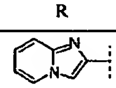
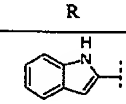
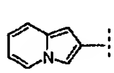
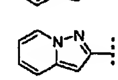
Synthesis

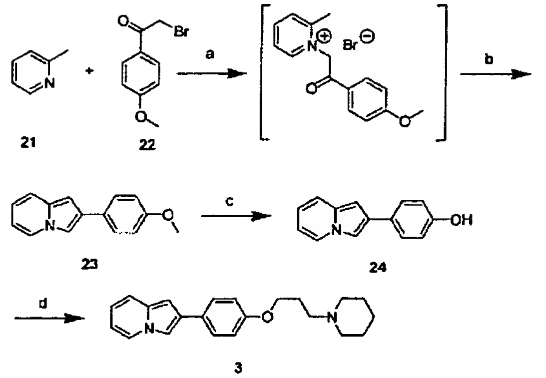
Syntheses of indolizine compounds (**3–17**) were accomplished according to the procedure outlined in Scheme 1 for the preparation of **3**. 2-Picoline (**21**) was treated with α-bromoacetophenone (**22**) providing the 2-phenyl indolizine core **23**. Demethylation of **23** gave **24** which was condensed with 3-chloropropylpiperidine affording **3**.

The indole **19** was prepared according to Scheme 2. Phenylacetylene **25** was prepared from benzaldehyde **26** via initial protection of the phenol followed by acetylene formation[17] using the Seyferth/Gilbert reagent.[18] 2-Iodo-*N*-(methanesulfonyl)aniline **27** was obtained upon treating 2-iodo-aniline **28** with methansulfonylchloride. Palladium mediated coupling reaction[19] of **27** with **25** afforded the appropriately substituted indole core **29**. Removal of the MEM (2-methoxyethoxymethyl) protecting group and alkylation of the free phenol under Mitsunobu conditions[20] gave protected indole **19** which was converted to **18**.

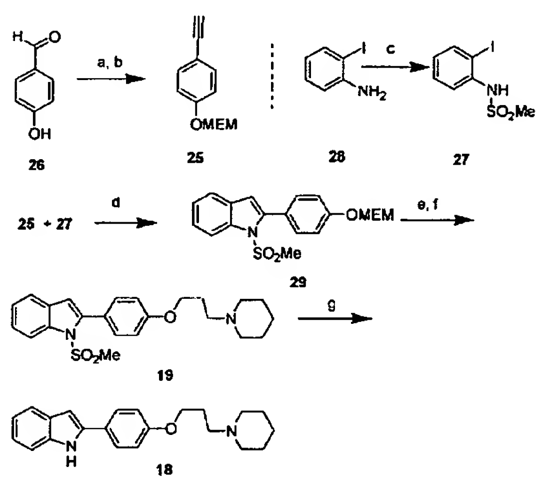
Table 3. Heterocycle variations



No.	R	K_i (nM)	No.	R	K_i (nM)
2		6 (±0.1)	18		47 (±6.4)
3		13 (±2.3)	20		11 (±1.2)



Scheme 1. Regents and conditions: (a) acetone, reflux, 1 h; (b) K_2CO_3/H_2O, 5 h, 99% (a and b two steps); (c) NaSEt/DMF, 100 °C; or HBr/HOAc, 100° C, 1 h; (d) NaO*t*Bu/DMF, 3-chloropropylpiperidine, 100° C, 16 h, 93 or 90% (c and d two steps).

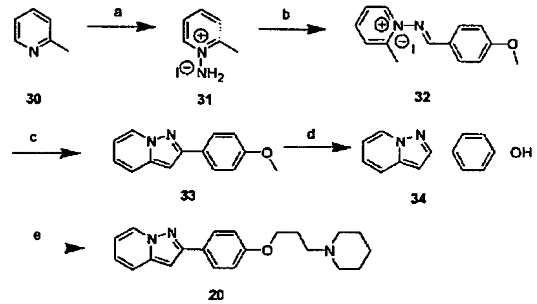


Scheme 2. Regents and conditions: (a) NaH, DMF, 1 h, rt; MEMCl, 16 h, rt, 87%; (b) $(MeO)_2POC(N_2)COMe$, K_2CO_3, MeOH, 18 h, rt, 82%; (c) MsCl (2 equiv), TEA, CH_2Cl_2, 2 h, 0 °C; KOH, 1:1 MeOH/H_2O, 1 h, rt, 74%; (d) $Pd(PPh_3)_2Cl_2$, CuI, 4:1 DMF/TEA, 18 h, 80 °C, 89%; (e) 2 N HCl, dioxane/MeOH, 1 h, rt, 81%; (f) DEAD, polymer-supported PPh_3, 3-hydroxypropylpiperidine, THF, 5 h, rt, 47%; (g) KOH, 1:1:1 THF/MeOH/H_2O, 12 h, rt, 20%.

Synthesis of pyrazolo[1,5-*a*]pyridine **20** was accomplished as shown in Scheme 3 using a published procedure[21] for the key ring construction sequence (**30**–**33**). Picoline **30** was aminated to **31**. Condensation of **31** with 4-methoxybenzaldhyde gave **32**. Cyclisation of **32** then provided 2-phenyl-pyrazolo[1,5-*a*]pyridine **33**. Demethylation of **33** gave **34** which was alkylated with 3-chloropropylpiperidine to afford **20**.

Biological Results and Discussion

The indolizines, exemplified by **3**, show comparable activity to imidazopyridine **2**. However the corresponding indole **18** is less potent. The pyrazolopyridine **20** is moderately potent and overall receptor affinity appears



Scheme 3. Reagents and conditions: (a) (i) HO_3SONH_2, H_2O, reflux, 1 h; (ii) K_2CO_3; (iii) HI, 23%; (b) *p*-methoxybenzaldes, MeOH, reflux, 20 h; (c) I_2, pyridine, 6 h, reflux, 10% (b and c two steps); (d) HBr/HOAc, 100 °C, 3 h, 80%; (e) NaO*t*Bu/DMA, 3-chloropropylpiperidine, 100 °C, 16 h, 42%.

to be dictated by the basicity of the fused heterocycle. Indolizine **3** was examined in more detail and exhibited high selectivity with respect to a range of G-protein coupled receptors, ion-channels and transporters. (Inactive at concentrations below 500 nM). Its permeability (Caco-2) is high (Papp = 14.1 × 10^6 cm/s). In a functional assay versus the human H_3 receptor using SKNMC cells stably transfected with the human H_3 receptor **3** yielded a pA_2 = 8.5. The rat pA_2 was observed to be 7.71. In contrast to imidazopyridine **1**, indolizidine **3** exhibited less binding to human serum albumin, 50% versus >90%, respectively. However whilst **3** showed a very favorable potency, selectivity and pharmacokinetic profile we were disappointed to observe rapid metabolism when **3** was exposed to human liver microsomes ($t_{1/2} \sim 10$ min). Therefore we chose to examine additional compounds and found that the introduction of an alkyl group (e.g., **5**) afforded a compound with superior stability ($t_{1/2} \sim 54$ min) without loss of potency.

In conclusion, the imidazopyridine nucleus of **2** may be replaced by alternative fused heterocycles to afford potent histamine H_3 receptor antagonists that exhibit favorable properties for further development as therapeutic agents.

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16. The calculated proton affinities for **2**, **3**, **18**, and **20** are −242.09, −236.51, −220.08 and −228.89 kcal/mol, respectively. These data gave a good correlation with the measured K_i's in Table 3 with an $R^2 = 0.827$. The sites of protonation for the heterocycles were N-1, C-3, C-3, and N-1 for compounds **2**, **3**, **18**, and **20**, respectively. The proton affinities were calculated at the B3LYP/cc-pVTZ(-f)++//B3LYP/6-31G** level of theory using Jaguar 4.1, Schrodinger Inc, Portland, OR, 1991–2000.
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